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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,893	EISEN, ANDREW	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-19* is/are pending in the application.

4a) Of the above claim(s) *9,11,13-15 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *8,10,12,16,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 July 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 Jan 2002
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants preliminary amendment of canceling claims 1-73, amending claims 74 and 81 and adding new claims 88-103, Paper No. 9, 3/18/2003, is acknowledged. Claims 74, 76-79, 81 and 88-103 are at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 8, 10, 11, 18 and 19 in Paper No. 11 is acknowledged. Applicants request for the modification of those claims included in Group I to include in addition to claims 8, 10, 18 and 19, claims12 and 16 instead of claim 11 is acknowledged. Originally, claims 12 and 16 were placed in Group III directed to a method of using the DRAP polypeptide for targeting mutagenesis and claim 11 was directed to a method of using the DRAP polypeptide for isolating genomic DNA. The substitution of the method claims 12 and 16 for the method claim 11 in the elected Group I is accepted . Thus applicants election of Group I, now claims 8, 10, 12, 16, 18 and 19 is acknowledged.

Applicant further traverses the restriction requirement and requests rejoinder of all claims on the basis that contrary to the examiner's previously stated position, the inventions set forth in Groups I through VII do in fact "form a Single inventive concept" under PCT Rule 13.1, because there is a "technical relationship" among the inventions "involving" a "special technical feature" and each of the inventions identified by the examiner involve the same or corresponding special technical feature in that they all rely on the DRAP polypeptide. Applicants argument is not found persuasive because it is the office's position that the technical feature to which applicant's refer, the "DRAP

polypeptide", is taught by Eisen et al. (A recombinase from *Drosphila melanogaster* embryos, PNAS, Vol 85, pp 7481-7485, October 1988), thus the proposed technical feature is not a "special" technical feature and unity between the groups is thus lacking.

It is noted that pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), upon the determination of allowable product claims, those claims subject to rejoinder may then be rejoined.

Applicants further note that during the international phase of the present application the USPTO, acting in its capacity as the International Search and Examination Authority, did not make a lack of unity on claims that were identical to claims 8-19. Applicants comments are acknowledged, however, as pointed out to applicants above, such a lack of unity could have been made previously, as the "DRAP polypeptide", is taught by Eisen et al. (A recombinase from *Drosphila melanogaster* embryos, PNAS, Vol 85, pp 7481-7485, October 1988), thus the proposed technical feature is not a "special" technical feature and unity between the groups is thus lacking.

The requirement is still deemed proper and is therefore made FINAL.

Claims 9, 11, 13-15 and 17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 11.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other

information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosures, filed 1/22/2002, and Paper No. 10, filed 5/8/2003, is acknowledged. Those references considered have been initialed.

Drawings

The drawings objected to for the reasons stated on the Form PTO-948. Note, applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Claim Objections

Claims 10, 12 and 16 are objected to because of the following informalities:

Claims 10, 12 and 16 each recite "DRAP". It is suggested that the first time applicants recite "DRAP" in the claims, that applicants write out "Drosphila Recombination Associated Protein" followed by "DRAP" in parenthesis.

Claim 10 is objected to because the recitation "A fragment of a DRAP polypeptide" is unclear given the above objection of claims 10, 12 and 16. If DRAP stands for "Drosphila Recombination Associated Protein", then this recitation in claim 10 is "A fragment of a **Drosphila Recombination Associated Protein** polypeptide". Specifically, the reference to a "...Protein polypeptide" is confusing and it is suggested that consistency be maintained throughout the application.

Appropriate correction or explanation is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 10 is rejected under 35 U.S.C. § 101 because the claimed invention is directed toward non-statutory subject matter. In the absence of the hand of man, naturally occurring Insert and press F9~are considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). This rejection may be overcome by amending the claims to contain wording such as "An isolated and purified fragment of a DRAP polypeptide of SEQ ID NO: 4 or a function-conservative variant..." .

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 12 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10, 12 and 16 are indefinite in that it is unclear what applicants intend to be encompassed by a "DRAP polypeptide" as the specification fails to teach which

identifying characteristics distinguish a "DRAP polypeptide" from other polypeptides. This rejection goes beyond the above discussed issue under the "claim objections", The application teaches many characteristics of the disclosed proteins (for example, possessing recombinase and topoisomerase activity etc.) but fails to define which of these are necessary for inclusion of a protein which is distinct in sequence from SEQ ID No: 4 to be considered to be within this class.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 12 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 10, 12 and 16 are directed to all possible function-conservative variants of a DRAP polypeptide of SEQ ID NO: 4, that carries out recombinase/topoisomerase activity associated with the DRAP protein and all possible methods for targeting mutagenesis or of promoting gene disruptions of a defined DNA segment comprising introducing any DRAP and an oligonucleotide homologous to said DNA segment into a cell (claims 12 and 16).

The specification, however, only provides the single representative species isolated from *Drosphila melanogaster* embryos having the amino acid sequence of SEQ

ID NO: 4, encompassed by these claims, and methods of the use of this specific DRAP. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these enzymes by any identifying structural characteristics or properties other than the activities recited in claims 10, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov. Claims 10, 12 and 16

Claims 10, 12 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DRAP polypeptide comprising the amino acid sequence defined by SEQ ID NO: 4, does not reasonably provide enablement for any function-conservative variant of a DRAP polypeptide of SEQ ID NO: 4 having recombinase/topoisomerase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir.

1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 10, 12 and 16 are so broad as to encompass any function-conservative variants of a DRAP polypeptide of SEQ ID NO: 4, that carries out recombinase/topoisomerase activity associated with the DRAP protein and all possible methods for targeting mutagenesis or of promoting gene disruptions of a defined DNA segment comprising introducing any DRAP and an oligonucleotide homologous to said DNA segment into a cell (claims 12 and 16). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DRAP polypeptides broadly encompassed by the claims, including all DRAPs and variants thereof. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the DRAP or the function-conservative variants of said DRAP. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited

to that DRAP isolated from *Drosphila melanogaster* embryos having the amino acid sequence of SEQ ID NO: 4.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DRAP because the specification does not establish: (A) regions of the protein structure which may be modified without effecting recombinase/topoisomerase activity; (B) the general tolerance of DRAP to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of DRAP with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the recombinase/topoisomerase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g.,

see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having the claimed recombinase/topoisomerase activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any DRAP. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Eisen et al. (Proc. of the Nat. Acad. Sci. USA, Vol 85, pp. 7481-7485, October 1988, See IDS ref 10).

Eisen et al. teach the purification of a recombinase from *Drosphila melanogaster* embryos. Eisen et al. further teach a method comprising introducing DRAP and an oligonucleotide homologous to a double stranded DNA. Thus Eisen et al. anticipate claims 8 and 10 drawn to an isolated polypeptide comprising the amino acid sequence defined by SEQ ID NO: 4 or a fragment or function-conservative variant of said polypeptide.

Claims 18 and 19 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Eisen et al. (Proc. of the Nat. Acad. Sci. USA, Vol 85, pp. 7481-7485, October 1988, See IDS ref 10.

As discussed above, Eisen et al. teach the purification of a recombinase from *Drosphila melanogaster* embryos. Eisen et al. further teach a method comprising introducing DRAP and an oligonucleotide homologous to a double stranded DNA. Thus Eisen et al. anticipate claims 8 and 10 drawn to an isolated polypeptide comprising the amino acid sequence defined by SEQ ID NO: 4 or a fragment or function-conservative variant of said polypeptide. Eisen further teach a 31-fold purification of the DRAP was achieved in one chromatographic step, and subsequently this purified DRAP was further purified through the use of several more columns. Thus the protein sample taught by Eisen et al. comprises DRAP, which inherently has the amino acid sequence of SEQ ID

NO: 4, wherein said DRAP comprises at least 10% by weight of the total protein in the sample, thus anticipating claims 18 and 19.

In the event that the protein sample comprising the purified DRAP is not 10% by weight of the total protein in the sample, one of ordinary skill in the art would have been motivated to purify the taught DRAP to homogeneity. The advantages of purifying proteins such as DRAP, to homogeneity are well known to those of ordinary skill in the art. These include: higher specific activities of purified materials allow smaller quantities of enzyme solution to be used, prevention of unwanted reactions with impurities in crude solutions, removal of possible inhibitors in crude solutions, etc. This would have clearly provided motivation for one of ordinary skill in the art to purify the DRAP taught by Eisen et al. The reasonable expectation of success comes from the high degree of skill and knowledge in the art of protein purification especially in light of the identification and taught partial purification by Eisen et al who also teach an assay which may be used to monitor the further protein purification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eisen et al. (Proc. of the Nat. Acad. Sci. USA, Vol 85, pp. 7481-7485, October 1988, See IDS ref 10) and Zarling et al. (U.S. Patent No. 5,763,240, issued 6/9/1998).

As discussed above, Eisen et al. teach the purification of a recombinase from *Drosphila melanogaster* embryos. Eisen et al. further teach a method comprising introducing DRAP and an oligonucleotide homologous to a double stranded DNA. Thus Eisen et al. anticipate claims 8 and 10 drawn to an isolated polypeptide comprising the amino acid sequence defined by SEQ ID NO: 4 or a fragment or function-conservative variant of said polypeptide.

Zarling et al. teach methods for targeting an exogenous polynucleotide to a predetermined endogenous DNA target sequence in a eukaryotic cell by homologous pairing. Specifically Zarling et al. teach a method for targeting mutagenesis of a defined segment of DNA in a eukaryotic cell comprising introducing into a cell at least one recA recombinase and at least two single stranded targeting polynucleotides (oligonucleotide)(See claim 1 of 5,763,240). Zarling et al. teach that the encompassed recA recombinase may be any of a family of RecA-like recombination proteins all having essentially all or most of the same functions, specifically i) the ability to properly position targeting polynucleotides on their homologous targets, and ii) the ability of the recA protein/targeting polynucleotide complex to find and bind to the complementary endogenous sequences.

One of ordinary skill in the art would have been motivated to practice the taught methods for targeting an exogenous polynucleotides to a predetermined endogenous

DNA target sequence of Zarling et al. using any recA-like protein family member as defined by Zarling et al. (i.e. having i) the ability to properly position targeting polynucleotides on their homologous targets, and ii) the ability of the recA protein/targeting polynucleotide complex to find and bind to the complementary endogenous sequences.). Eisen et al. teach such a protein with these defined functional characteristics, and thus one would have been motivated to use the protein taught by Eisen et al. in the method of Zarling et al. The reasonable expectation of success comes from the high degree of knowledge in the art of protein purification with respect to isolating a protein which has been identified and for which an assay to monitor the protein exists, as well as the teachings of Zarling et al. who teach the isolation of similar recombinase proteins.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
August 7, 2003